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SYNTHESIS AND TRANSGLYCOSYLASE-INHIBITING PROPERTIES OF A DISACCHARIDE ANALOGUE OF MOENOMYCIN A LACKING SUBSTITUTION AT C-4 OF UNIT F

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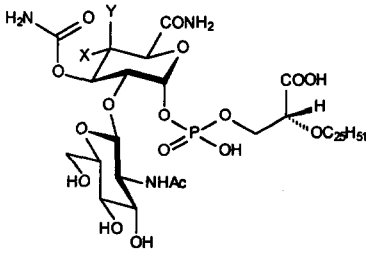
Abstract - A disaccharide analogue (**A4** = **13c**) of moenomycin A lacking the OH group in the 4-position of the uronic acid moiety has been synthesized using the Saito deoxygenation reaction as key step. **13c** does not inhibit the transglycosylase (PBP 1b), a key enzyme in the biosynthesis of bacterial peptidoglycan. The result demonstrates the importance of this OH group for the binding of disaccharide moenomycin analogues to the enzyme.

Key words: Antibiotics, carbohydrates, phospholipids, structure-activity, radical deoxygenation

Introduction

Recently we have comprehensively discussed what is known about the structure-activity relationships of transglycosylase inhibitors of the moenomycin-type[1] and have outlined a mechanistic proposal for the inhibition of the enzyme.[2] In the series of disaccharide analogues the OH group in the 4-position of unit F seems to play an important role. Whereas compounds **A1**[3] and **A2**[1] inhibit the penicillin-binding protein (test of van Heijenoort) compound **A3** with D-*galacto* configuration in unit F



A	X	Y
1	OH	CH_3
2	OH	H
3	H	OH
4	H	H

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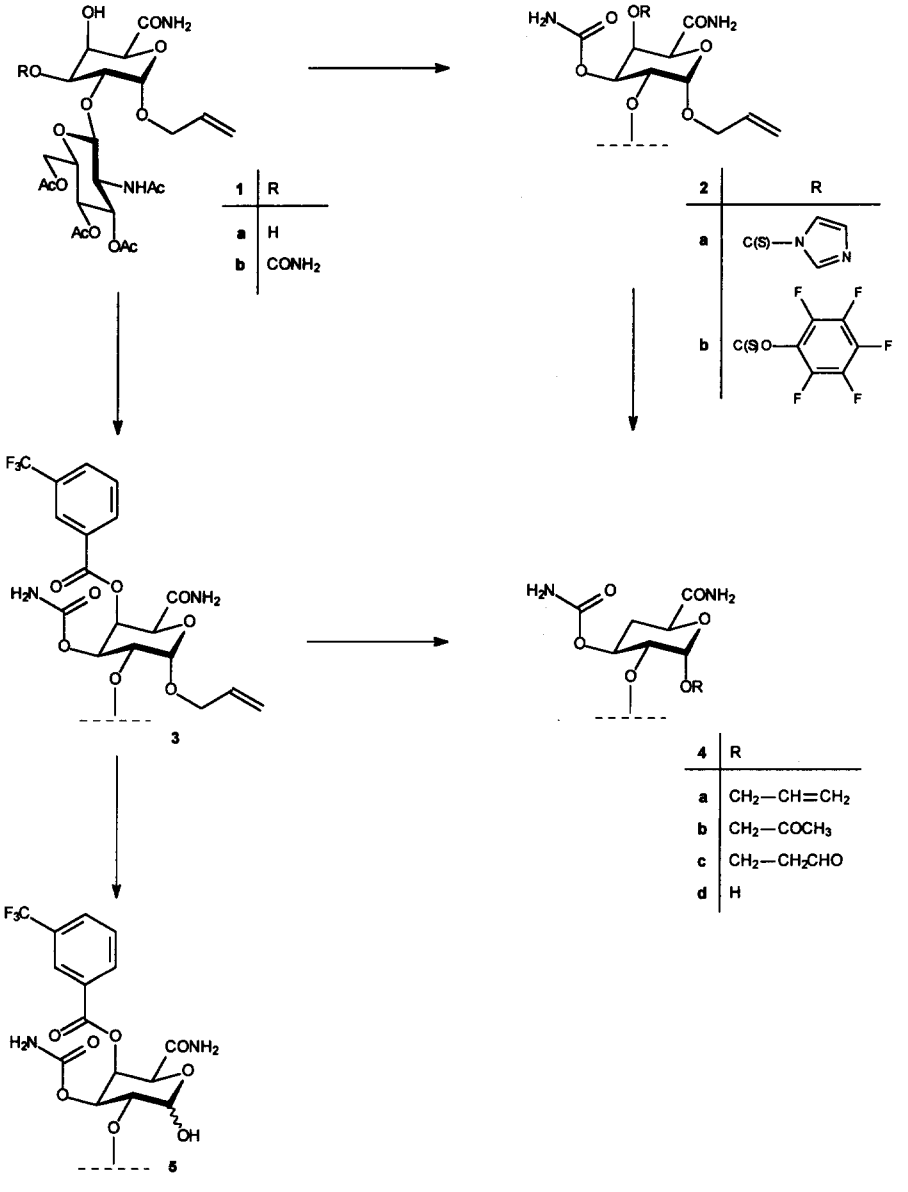
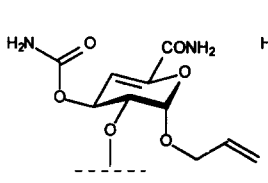
is inactive.[4] It was the purpose of the work discussed below to prepare the 4-deoxy analogue **A4** in order to confirm that it is the equatorial OH group in compounds **A1** and **A2**, respectively, that is essential for eliciting transglycosylase-inhibiting properties.



Barton deoxygenation of 1b

In model experiment deoxygenation reactions of the S_N2-type proved fruitless.[5] We decided, therefore, to concentrate on radical deoxygenations.[6] Starting material for the deoxygenation experiments was **1b** which was prepared from **1a** by (i) reaction with bis(tributyltin)oxide to yield a stannyl ether, (ii) treatment of the stannyl ether with trichloroacetyl isocyanate to give the trichloroacetyl urethane, and (iii) subsequent reductive removal of the trichloroacetyl group. We have described this somewhat capricious sequence of reactions previously.[4] By careful optimization we could now increase the overall yield to 98%. We then



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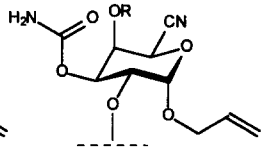
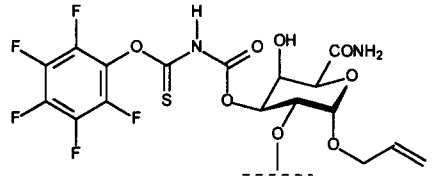


7	R
a	H
b	CO—C_6H_4—CF_3



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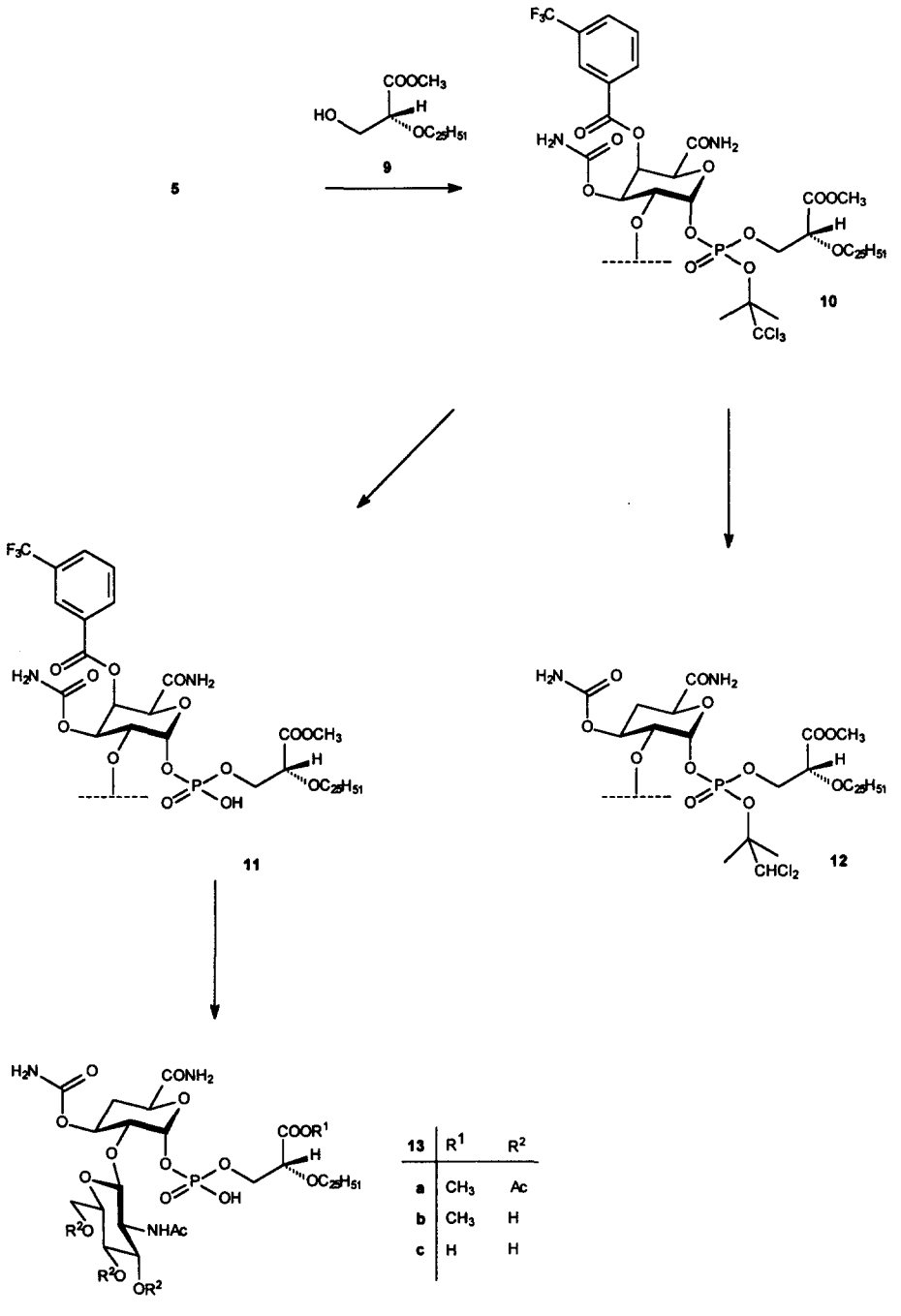
studied a number of the Barton deoxygenation reactions. First, **1b** was converted into **2a** by reaction with thiocarbonyl diimidazole and then treated with tributyltin hydride (Barton-McCombie reaction). Besides **4a** the unsaturated amide **6** was isolated. In the best experiments the yield of **2a** was 60% and that of **4a** 71%. Unfortunately, in different experiments the yields in both steps varied considerably and, in addition, both **2a** and **4a** could be purified only with difficulties. We then tried to convert **1b** into the pentafluorophenoxythiocarbonyl derivative **2b**.[7] In the event, reaction of **1b** with pentafluorophenoxythiocarbonyl chloride led (according to TLC) to the complete consumption of **2b** and formation of a new product. However, on work-up we reisolated the starting material **1b** and nitrile **7a** (20%). We could not find conditions which allowed to suppress the degradation of the intermediate product to furnish **1b** and **7a**. The ^1H NMR spectra of this compound indicated that no reaction at the 4-OH group had occurred. The uronamide functionality was also unchanged. The ^{19}F NMR spectrum showed the presence of the pentafluorophenyl unit and a ^{13}C signal at $\delta = 181$ was taken as an indication of presence of the C=S group. To us, **8** seems to be the most plausible structure of this intermediate. In view of the difficulties encountered with the Barton-McCombie reactions we seeked for alternatives.

Synthesis of 13c using the Saito deoxygenation as key step

Some time ago Saito published a deoxygenation reaction in which m-trifluoromethylbenzoates are reduced with N-methylcarbazole in the photoexcited state as an electron transfer reagent and isopropanol as the real reducing agent.[8] Thus, **1b** was converted to the m-trifluoromethylbenzoate **3** (88%) on reaction with the



corresponding acid chloride under carefully controlled conditions. Steglich's base had to be added, otherwise almost 30% of nitrile **7b** were formed. Photolysis of **3** in isopropanol-water solution in the presence of N-methylcarbazole and magnesium perchlorate furnished deoxygenation product **4a** in 95% yield. The

irradiation was performed at 257 nm by means of a Rayonet reactor using quartz vessels. The isolation of **4a** was best performed using gel permeation chromatography to separate the highly polar carbohydrate from magnesium perchlorate. Removal of the allyl protecting group[9] from **4a** turned out to be another difficult step. The widely used Ir(I)- mediated rearrangement[10] of the allyl to a propenyl group met with failure as a consequence of the high polarity of **4a**. We then applied our two-step procedure[11] consisting of (i) a Wacker oxidation to give **4b** and **4c** and (ii) conversion of the Wacker products to the free sugar **4d**. β-Alkoxy aldehyde **4c** readily decomposed even under the Wacker and working-up conditions to yield **4d**. The mixture consisting of all three compounds was irradiated in the presence of triethylamine. Under these conditions **4b** was cleaved via electron transfer in the photoexcited state.[11] The overall yield of **4d** was 44%. We also studied the deallylation using Nakayama's procedure[12] (freshly prepared $(Ph_3P)_4Pd$ in acetic acid). We had great problems in purifying **4d** due to its high polarity. In view of these problems we decided to postpone the deoxygenation to a later step in the synthesis.

Thus, **3** was deallylated by means of the Nakayama method to provide **5** in 83% yield. In this case purification (removal of Pd and phosphorous species) was straightforward but still required two chromatographic separation steps. **5** and **9** (obtained by degradation from moenomycin[13]) were converted into phosphoric acid triester **10** using the phosphite methodology in the optimized version for moenomycin-type compounds[14] (58% yield). Application of the Saito protocol to **10** led to the formation of **12** (47%). On prolonged reaction times some **13a** was obtained. Unfortunately, the $C(CH_3)_2$-$CHCl_2$ could not be removed from **12** with Zn-Cu couple under the normal Imai conditions[15] to give **13a**. This meant that still another route had to be followed. Thus, first the trichloroethyl-type phosphate protecting group was removed from **10** with Zn-Cu couple in pyridine in the presence of 2,4-pentanedione (Imai conditions[15]) to provide **11** in 100% yield. Subsequent Saito deoxygenation converted **11** into **13a** in 68% yield. Success of the reaction was indicated by the appearance of a new signal complex belonging to CH_2-4^F and absence of the m-trifluoromethybenzoyl signals. Finally, **13a** on hydrolytic cleavage of the ester protecting groups gave the target compound **13c**. After short reaction times methyl ester **13b** could be isolated.

Transglycosylase-inhibiting properties of 13c

Even at a concentration of 10 μg / ml **13c** had no inhibitory effect on the transglycosylase (determined by the in-vitro assay which uses a crude extract from an over-producer of polymerase PBP 1b {E.coli JA200plc19-19}) and as substrate lipid II which is the immediate precursor of un-crosslinked peptidoglycan.[16]

Conclusions

The synthesis of **13c** has shown the limitations of well-established radical deoxygenation reactions in special cases and proved the feasibility of the Saito method under these circumstances.

Furthermore, it was demonstrated, in connection with the results summarized in the Introduction, that the equatorial hydroxyl function at C-4 of unit F in compounds **A1** and **A2** plays a very important role in the interaction of the disaccharide transglycosylase inhibitors with the enzyme. Inverting the configuration at C-4 or removing the 4-OH group leads to compounds devoid of transglycosylase inhibiting properties.

Experimental

General

Instrumentation: NMR: Gemini 200 and Gemini 2000 (Varian, ^{1}H NMR 200 MHz, ^{13}C NMR 50.3 MHz), Gemini 300 (Varian, ^{1}H NMR 300 MHz, ^{13}C NMR 75.5 MHz, ^{31}P NMR 121.5 MHz, ^{19}F 282.3 MHz), Unity 400 (Varian, ^{1}H NMR 400 MHz, ^{13}C NMR 100.6 MHz, ^{31}P NMR 161.9 MHz) or AM 400 (Bruker), chemical shifts are given in δ values, CH_3, CH_2, CH groups and quaternary carbons were identified by APT (attached proton test); the ^{31}P NMR shifts are based on external phosphoric acid; FAB MS: VG AUTOSPEC (Cesium ion gun, 30 keV, matrix: lactic acid or 3- nitrobenzyl alcohol), MALDI-TOF MS: Voyager DE™ RP (PerSeptive Biosystems, matrix: α-cyano-4-hydroxycinnamic acid); two molecular masses are always communicated, the first was calculated using the International Atomic Masses, the second refers to ^{12}C, ^{1}H, ^{16}O, ^{14}N, ^{31}P, ^{35}Cl, ^{120}Sn (mono-isotopic masses), carbon and proton numbering in the subunits (see NMR data) as well as naming of the MS fragments follows the moenomycin nomenclature;[3] FT-IR: ATI Mattson Genesis; lyophilization: GT2 (Leybold-Heraeus) and Alpha1-2 (Christ); normal phase TLC: Merck precoated silica gel $60F_{254}$ plates, 0.2 mm; reversed-phase TLC: Merck RP-18, F_{254S}, 0.2 mm; spots were identified under a UV lamp (λ= 254 and 366 nm) and with p-anisaldehyde (1 ml) and conc. H_2SO_4 (4 ml) in ethanol (95 ml); flash chromatography (FC): silica gel 32–63 μm (ICN Biomedicals), the samples were dissolved in a small amount of the eluent or dissolved in a suitable solvent and deposited on kieselguhr (Fa. Merck); gel filtration: Sephadex G-10 (Pharmacia); medium-pressure liquid chromatography (MPLC): silica gel 20-40 μm (Merck), 35-70 μm (Amicon) or 50 μm (Fa. Grace), the samples were applied to a precolumn (3-5 g Kieselgel, 63-100 μm) and eluted at $1\text{-}2\cdot10^5$ Pa using a dosage pump (Promint Dosiertechnik, Heidelberg or Kronlab Chromatographie und Labortechnik, Sinsheim).- Dry solvents were prepared using standard procedures, 4Å molecular sieves were activated at 320°C and 10 Pa; moisture- and O_2-sensitive reactions were performed in an argon atmosphere using preheated reaction vessels sealed with septa or the Schlenk technique.- For the photochemical experiments irradiation was performed using a Hg high pressure lamp (Philips HPK 125 W) through pyrex at 20°C under argon (using an usual photochemical immersion reactor with a gas fritte, Hans Mangels, D-53332 Bornheim) or the Rayonet Photochemical Reactor RPR 100 at 257.3 nm (with quartz vessels equiped with a gas inlet at the bottom) were used. If necessary solutions were degassed by sonication (Bandelin, Sonorex Super RK 106). Dowex 50 WX 2 was regenerated with 5 per cent HCl and was then washed neutral with bidistilled water. $Pd(PPh_3)_4$ was prepared according to ref.[17]

Hydrogenation of the Flavomycin complex®

Progress of the reaction (performed as described previously[13]) was monitored by RP TLC (acetonitrile-methanol-water 1:6:3); R_F of the Flavomycin® complex: 0.20 and of the hydrogenation product: 0.14.

Allyl 2-*O*-(acetamido -3,4,6-tri-*O*-acetyl-2-deoxy -β-D-glucopyranosyl)-3-*O*-carbamoyl-α-D-galactopyranosiduronamide (1b)

A suspension of **1a** (0.377 g, 0.623 mmol, dried at 45°C at 10 Pa) in $CHCl_3$ (washed several times with water, dried first with $MgSO_4$ and then over P_4O_{10}, and distilled from P_4O_{10} in an argon atmosphere, 300 ml) was sonicated under argon for 30 min. Bis(tri-butyltin) oxide (0.563 g, 0.944 mmol) was added and the mixture was refluxed until a clear solution resulted (1 h). The refluxing solvent was dried with 4 Å molecular sieves. The clear solution was cooled to 0°C and trichloroacetyl isocyanate (0.27 g, 1.435 mmol) was added. The mixture was left at 0°C for 1 h. Excess reagent was destroyed with methanol (1 ml). Solvents were evaporated and the residue was dried, then taken up in methanol (70 ml). Zinc dust (449 mg) was added and the mixture was stirred at 20°C overnight. Excess methanol was added to dissolve solids and the residue was carefully washed with hot methanol. From the combined solutions solvents were removed by distillation. The residue was redissolved in hot methanol and mixed with silica gel. After solvent evaporation the mixture was washed with $CHCl_3$–MeOH 9:1 and then the product was eluated from the silica gel with pyridine to give after solvent evaporation 398.2 mg of **1b** (98%).- For spectral data, see ref.[4]

Reaction of 1b mit *N,N'*-thiocarbonyldiimidazole

With protection from light to a suspension of disaccharide **1b** (230.3 mg, 0.380 mmol) in DMF (494 µl, sonication) 1,2-dichloroethane (10.8 ml) and a solution of *N,N'*-thiocarbonyldiimidazole (248.3 mg, 1.254 mmol) in 1,2-dichloroethane (5.0 ml) was added. The reaction mixture was stirred at 85°C for 20 h. Solvent evaporation and medium pressure liquid chromatography MPLC (B column, PE-$CHCl_3$-EtOH 1:1:0.4→1:1:1, protection from light) provided **2a** (164.2 mg, 60%) and a fraction containing impure **1b** (31.2 mg).

Allyl 2-*O*-(2-acetamido-3,4,6-tri*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-3-*O*-carbamoyl-4*O*-(imidazolylthiocarbonyl)-α-D-galactopyranosiduronamide (2a)

IR (CH_3CN): 3640, 3500, 3380, 1750, 1705, 1600 cm^{-1}.- ^1H NMR (400 MHz, pyridine-d_5): *unit E*, δ = 1.98, 2.00, 2.02, 2.10 ($COCH_3$), 5.69 (d, 1-H), 4.00 (ddd, 2-H), 6.11 (dd, 3-H), 5.37 (dd, 4-H), 3.85 (dt, 5-H), 4.39 (d, 6-H, 6-H'), 9.03 ($N\underline{H}COCH_3$), $J_{1,2}$ = 8.5 Hz, $J_{2,3}$ = 10 Hz, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 10 Hz, $J_{5,6}$ = $J_{5,6'}$ = 3.5 Hz, $J_{2,NH}$ = 8 Hz; *unit F*, δ = 5.74 (d, 1-H), 4.65 (dd, 2-H), 6.23 (dd, 3-H), 7.29 (dd, 4-H), 5.11 (d, 5-H), 8.12 (s, b, $CONH_2$), 8.62 (s, b, $CONH_2$), $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.0 Hz; *allyl signals*,[18] δ = 4.23 (ddd, 1-H), 4.30 (ddd, 1-H'), 5.9-6.0 (m, 2-H), 5.10 (ddd, 3-H^{cis}), 5.33 (ddd, 3-H^{trans}), $J_{1,1'}$ = 13.5 Hz, $J_{1,2}$ = 5.8 Hz, $J_{1',2}$ = 5.5 Hz, $J_{1,3}$ = 1.5 Hz, $J_{2,3trans}$ = 17.5 Hz, $J_{2,3cis}$ = 10.5 Hz, $J_{3cis,3trans}$ = 3 Hz; imidazole unit, δ = 7.02 (s), 7.71 (s), 8.59 (s).- ^{13}C NMR (100 MHz, pyridine-d_5): δ = 184.40, 171.03, 170.60, 170.50, 169.92, 169.54 (CO), 157.04 ($OCONH_2$), 137.33 ($C^{imidazole\ unit}$), 134.44 ($C\text{-}2^{allyl}$), 131.27 ($C^{imidazole\ unit}$), 118.78, 117.49 ($C\text{-}3^{allyl}$, $C^{imidazole\ unit}$) 102.10 ($C\text{-}1^{E}$), 99.06 ($C\text{-}1^{F}$), 56.42 ($C\text{-}2^{E}$), 80.21, 76.54, 72.65, 72.08, 70.43, 69.81, 69.81, 69.40 ($C\text{-}3^{E}$, $C\text{-}4^{E}$,$C\text{-}5^{E}$, $C\text{-}5^{F}$, $C\text{-}4^{F}$, $C\text{-}3^{F}$, $C\text{-}2^{F}$, $C\text{-}1^{allyl}$), 62.52 ($C\text{-}6^{E}$), 23.34 ($NHCO\underline{C}H_3$), 20.76, 20.64, 20.57 ($OCO\underline{C}H_3$).- $C_{28}H_{37}N_5O_{15}S$ (715.69, 715.20), FAB MS: m/z = 716.0 ($[M+H]^+$), 330.0 ($[e]^+$).

Allyl 2-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-3-*O*-carbamoyl-4-deoxy-α-D-*xylo*-hexopyranosiduronamide (4a)

To a solution of **2a** (22.2 mg, 31 µmol) in acetonitrile (1.2 ml) tri-n-butyltin hydride (22 µl, 23.1 mg, 79 µmol) and a solution of AIBN (1 mg, 6 µmol) in acetonitrile (16 µl) were added. The reaction mixture

was heated at 100°C for 5 h with protection from light. Solvents were distilled off and the residue was extracted with petroleum ether and methanol. The methanol solution was evaporated and the residue separated by LC (PE-$CHCl_3$-MeOH 1:1:0.3) to provide **4a** (12.7 mg, 71%)- IR (KBr): 3640-3120, 2963, 1742 (C=O), 1678 ($CONH_2$), 1551, 1379, 1331, 1236, 1043, 939 cm^{-1}.- ^1H NMR (400 MHz, pyridine-d_5 (C,H COSY; H,H COSY, some impurity signals appeared in the spectra): *unit E*, δ = 5.63 (d, 1-H, $J_{1,2}$ = 8.2 Hz), 3.95-4.00 (m, 2-H), 6.14 (dd, 3-H, $J_{2,3} = J_{3,4}$ = 9.7 Hz), 5.37 (dd, 4-H, $J_{3,4} = J_{4,5}$ = 9.7 Hz), 3.95-4.00 (m, 5-H), 4.41 (dd, 6-H, $J_{5,6}$ = 2.5 Hz), 4.49 (dd, 6-H', $^2J_{6,6'}$ = 12.3 Hz, $J_{5,6'}$ = 4.4 Hz), 2.00, 2.01, 2.04 (3*s, 3*$COCH_3$), 2.15 (s, $NHCOCH_3$), 9.07 (d, $NHCOCH_3$, $J_{NH,2}$ = 6.0 Hz); *unit F*, δ = 5.46 (d, 1-H, $J_{1,2}$ = 3.2 Hz), 4.02 (dd, 2-H, $J_{2,3}$ = 10.0 Hz), 5.74 (ddd, 3-H, $J_{2,3} = J_{3,4ax}$ = 10.0 Hz, $J_{3,4eq}$ = 5.1 Hz), 1.94 (m, 4-H_{ax}), 3.15 (m, 4-H_{eq}), 4.66 (dd, 5-H, $J_{4ax,5}$ = 12.3 Hz, $J_{4eq,5}$ = 2.4 Hz), 7.85 (s, b, $CONH_2$), 8.33 (s, b, $CONH_2$).-^{13}C NMR (100.6 MHz, pyridine-d_5,C,H COSY; DEPT): *unit E*, δ = 101.95 (C-1), 56.29 (C-2), 72.6 (C-3), 69.83 (C-4), 71.92 (C-5), 62.47 (C-6), 20.46, 20.52, 20.60 (3*$CO\underline{C}H_3$), 23.27 ($NHCO\underline{C}H_3$), 170.41, 170.50, 171.11, 173.08 (4*$\underline{C}OCH_3$); *unit F*, δ = 99.04 (C-1), 79.9 (C-2), 69.39 (C-3), 35.36 (C-4), 68.28 (C-5), 169.84 ($CONH_2$), 157.37 ($OCONH_2$).- $C_{24}H_{35}N_3O_{14}$ (589.55, 589.21), calc: C 48.90 H 5.98, found: C 48.94 H 5.87, FAB MS (lactic acid): m/z = 590.1 ($[M+H]^+$), 330.1 ($[e]^+$).

Reaction of 1b with pentafluorophenoxythiocarbonyl chloride

At 20°C to a solution of **1b** (33.5 mg, 55 μmol) in pyridine (2.9 ml) pentafluorophenoxythiocarbonyl chloride was added in three portions (9 μl, {14.4 mg, 55 μmol}, 9 μl, {55 μmol} after 3.5 h, 9 μl, {55 μmol} after another 3.5 h). After a total reaction time of 25 h the reaction was stopped by addition of 2-propanol (15 μl). The mixture was stirred at 20°C for 4 h. Dichloromethane was added and the solution was washed with water and brine. Solvent evaporation (codistillation with toluene) and LC (silica gel (4 g) covered with Florisil® (1 g), PE-$CHCl_3$-EtOH 1:1:0.4 → 1:1:0.7) provided **8** (27.3 mg), **7** (1.3 mg); 24.0 mg of **1b** were recovered.

Compound 8 (tentative structure)

^1H NMR (400 MHz, pyridine-d_5): *unit E*, δ = 5.68 (d, 1-H, $J_{1,2}$ = 8.5 Hz), 3.97 (dd, 2-H), 6.14 (dd, 3-H, $J_{2,3} = J_{3,4}$ = 10.0 Hz) 5.39 (dd, 4-H, $J_{3,4} = J_{4,5}$ = 10.0 Hz), 3.72-3.80 (nm, 5-H), 4.29 (dd, 6-H, $^2J_6$ = 12.0 Hz, $J_{5,6}$ = 2.0 Hz), 4.48 (dd, 6-H', $J_{5,6'}$ = 4.0 Hz) 1.98, 1.99, 2.03 (3*s, 3*$COCH_3$), 2.14, 2.14 (2*s, $NHCOCH_3$ (?)), 9.16 (d, $NHCOCH_3$, $J_{NH,2}$ = 8.0 Hz); *unit F*, δ = 5.56 (d, 1-H, $J_{1,2}$ = 3.5 Hz), 4.96 (dd, 2-H, $J_{2,3}$ = 10.6 Hz), 5.86-5.97 (dd, 3-H), 5.44 (nm, 4-H $w_{1/2}$ = 7.0 Hz), 4.87 (s, 5-H), 7.94, 8.58 (2*s, b, 2*$CONH_2$), 8.53 (dd).-^{13}C NMR (100.6 MHz, pyridine-d_5, some impurity signals were present): *unit E*, δ = 101.64 (C-1), 56.65 (C-2), 72.94 (C-3), 69.78 (C-4), 71.96 (C-5), 62.34 (C-6), 20.48, 20.56, 20.65 (3*$CO\underline{C}H_3$), 23.44 ($NHCO\underline{C}H_3$), 170.41, 170.54, 170.84, 171.97 (4*$\underline{C}OCH_3$); *unit F*, δ = 99.01 (C-1), 75.21, (C-2), 72.94 (C-3), 69.16 and 68.75 (C-4 and C-1^{all}), 73.28 (C-5), 169.66 ($CONH_2$), 155.93 ($OCONH_2$), 180.81 (probably C=S).- ^{19}F NMR (75.4 MHz, Bruker WP 80, 1:1 pyridine-d_5-$CDCl_3$): δ = -163.76 (dd, 2F, F_{meta}), -158.09 (dd, 1F, F_{para}, $J_{p,m}$ = 22.0 Hz), -153.46 (d, 2F, F_{ortho}, $J_{o,m}$ = 20.0 Hz).- C_{31} $H_{34}F_5N_3O_{16}S$ (831.68, 831.16), FAB MS (lactic acid): m / z = 330.1 ($[e]^+$).

Allyl 2-*O*-(2-acetamido -3,4,6-tri-*O*-acetyl-2-deoxy-β-glucopyranosyl)-3-*O*-carbamoyl-α-D-galactopyranosidurononitrile (7a)

IR (KBr): 3371, 1747, 1662, 1551, 1232 cm^{-1}.- ^1H NMR (400 MHz, H,H COSY, pyridine-d_5): *unit E*, δ = 5.61 (d, 1-H), 4.08 (ddd, 2-H), 6.05 (dd, 3-H), 5.37 (dd, 4-H), 3.80 (ddd,5-H), 4.48 (dd, 6-H), 4.27 (dd, 6-H')

9.08 (CONH), $J_{1,2}$ = 8.5 Hz, $J_{2,3}$ = $J_{3,4}$ = $J_{4,5}$ = 10 Hz, $J_{5,6}$ = 5 Hz, $J_{5,6'}$ = 2.5 Hz, $J_{6,6'}$ = 12 Hz, $J_{2,NH}$ = 8Hz; *unit F*, δ = 5.57 (d, 1-H), 4.83 (dd, 2-H), 5.70 (dd, 3-H), 5.00 (dd, 4-H), 5.32 (d, 5-H); *methyl groups*, δ = 2.15 (s, $NCOCH_3$), 2.03, 1.99, 1.98 (3*s, $OCOCH_3$).- ^{13}C NMR (100 MHz, C,H COSY, pyridine-d_5): *unit E*, δ = 102.16 (C-1), 56.28 (C-2), 72.79 (C-3), 69.70* (C-4), 72.08 (C-5), 62.40 (C-6), 23.37 ($NHCOCH_3$), 20.66, 20.60, 20.52 ($OCOCH_3$); *unit F*, δ = 99.53 (C-1), 75.23 (C-2), 71.07 (C-3), 68.88 (C-4), 63.68 (C-5), 157.45 ($OCONH_2$), 117.96 (CN); *carbonyl carbons*, δ = 171.02, 170.51, 170.45, 169.87.- $C_{24}H_{33}O_{14}N_3$ (587.54, 587.20), FAB MS: m/z = 588.0 ($[M+H]^+$), 330.0 ($[e]^+$).

Reaction of 1b with 3-(trifluoromethyl)-benzoyl chloride

a) To a solution of **1b** (15.4 mg, 25 μmol) in pyridine (0.8 ml) 3-(trifluoromethyl)-benzoyl chloride was added in two portions (4 μl, {5.4 mg, 26 μmol} and 4 μl, {5.4 mg, 26 μmol}, after 1.5 h). The reaction mixture was stirred at 20°C. After a total reaction time of 3.5 h the reaction was stopped by addition of 2-propanol (0.2 ml). The mixture was then stirred for 2 h. Solvent evaporation (codistillation with toluene) and LC (silica gel (3.5 g), covered with Florisil® (1 g), PE-CH_2Cl_2-2-PrOH 2:1:0.4) furnished **3** (12.2 mg, 64%), **7b** (5.5 mg, 28%) and 3.5 mg of a compound of unknown structure.

b) To a solution of disaccharide **1b** (107.7 mg, 0.178 mmol) and DMAP (39.5 mg, 0.320 mmol) in pyridine (7.2 ml) at 0°C slowly 3-(trifluoromethyl)-benzoyl chloride (41 μl, 55.6 mg, 0.266 mmol) was added. Then the reaction mixture was allowed to warm to ambient temperature and was stirred at 20°C for 1.5 h. Excess of the acid chloride was destroyed by addition of 2-propanol (2.9 ml, stirring at 20°C for 3 h). Solvent evaporation (codistillation with toluene) and LC as described above furnished **3** (122.1 mg, 88%) and 6.2 mg of a compound of unknown structure.

c) To a solution of **1b** (0.327 g, 0.541 mmol) in pyridine (25 ml) a solution of DMAP (0.119 g, 0.974 mmol) in dry pyridine (8 ml) was added. At 0°C 3-(trifluoromethyl)-benzoyl chloride was added dropwise in 3 portions (140 μl, 0.191 g; 0.920 mmol, 100 μl (0.138 g; 0.663 mmol) after 30 min and again after another 30 min). After a total reaction time of 75 min at 0°C (reaction control by TLC, $CHCl_3$–MeOH 3:1) excess of the acid chloride was destroyed by addition of methanol (3 ml, stirring for 30 min at 0°C). Solvent evaporation (codistillation with toluene) followed by FC ($CHCl_3$–MeOH 9:1) gave **3** (0.352 g, 83 %).

Allyl 2-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-3-*O*-carbamoyl-4-*O*-(3-(trifluoromethyl)-benzoyl)-α-D-galactopyranosiduronamide (3)

IR (KBr): 3640-3120, 2910, 1740 (C=O), 1690 ($CONH_2$), 1590, 1540, 1370, 1330, 1250, 1170, 1130, 1070 (C-F), 1030, 920, 750, 690 cm^{-1}.- ^1H NMR (400 MHz, pyridine-d_5, T = 299 K, H,H COSY bei T = 308 K): *unit E*, δ = 5.83 (d, 1-H, $J_{1,2}$ = 8.4 Hz), 3.92 (ddd, 2-H), 6.22 (dd, 3-H, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 9.2 Hz), 5.39 (dd, 4-H, $J_{4,5}$ = 10.0 Hz), 3.86 (dd, 5-H), 4.37 (dd, 6-H, $J_{5,6}$ = 2.6 Hz), 4.45 (dd, 6-H', $J_{5,6'}$ = 4.7 Hz, $^2J_{6,6'}$ = 12.0 Hz), 1.97, 2.00, 2.06 (3*s, 3*$COCH_3$), 2.09 (s, $NHCOCH_3$), 9.27 (d, $NHCOCH_3$, $J_{NH,2}$ = 7.6 Hz); *unit F*, δ = 5.76 (d, 1-H, $J_{1,2}$ = 3.6 Hz), 4.78 (dd, 2-H, $J_{2,3}$ = 10.6 Hz), 6.19 (dd, 3-H, $J_{3,4}$ = 3.7 Hz), 6.92 (dd, 4-H, $J_{4,5}$ = 1.6 Hz), 5.08 (5-H, hidden by the 3-H_{trans}^{allyl} signal), $CONH_2$ hidden by solvent signals; *3-trifluoromethylbenzoyl group*, δ = 8.38 (s, 2-H), 8.27 (d, J = 8.0 Hz) and 7.70 (d, J = 7.6 Hz, 4H and 6-H), 7.31 (dd, 5-H). At 308 K the 5-H^F signal was visible at δ = 5.06 and the two amide proton signals appeared at δ = 8.08 (d, 1H, $CONH_2$) and 8.54 (d, 1H, $CONH_2$).- ^{13}C NMR (75.4 MHz, pyridine-d_5, C,H COSY): unit *E*, δ = 101.78 (C-1), 56.41 (C-2), 72.23 (C-3), 69.65 (C-4), 71.80 (C-5), 62.26 (C-6), 20.32, 20.38, 20.47 (3*$CO\underline{C}H_3$), 23.09 $NHCO\underline{C}H_3$), 170.10, 170.21, 170.33, 170.86 (4*$\underline{C}OCH_3$); *unit F*, δ = 98.85 (C-1), 76.27 (C-2), 69.38 (C-3), 72.05 (C-4), 70.44 (C-5), 169.68 ($CONH_2$), 157.04 ($OCONH_2$); *3-trifluoromethylbenzoyl group*, δ = 131.42

(C-1), 126.52 (C-2, $^3J_{C,F}$ = 3.7 Hz), 130.40 (C-3, $^2J_{C,F}$ = 32.5 Hz), 133.29 and 129.44(C-4 and C-6), 129.55 (C-5), 124.02 (CF_3, $^1J_{C,F}$ = 272.6 Hz), 164.20 ($CO^{benzoyl}$).- ^{19}F NMR (282.3 MHz, pyridine-d_5): δ = 15.40, 15.60 (2*s, CF_3 signals, integration 3:1.)- $C_{32}H_{38}F_3N_3O_{16}$ (777.66, 777.22), FAB MS (3-nitrobenzyl alcohol): m/z = 800.3 ([M+Na]$^+$), 778.3 ([M+H]$^+$), 330.1 ([e]$^+$).

Allyl 2-*O*-(2-acetamido -3,4,6-tri-*O*-acetyl-2-deoxy -β-D-glucopyranosyl)-3-*O*-carbamoyl-4-*O*-(3-(trifluormethyl)-benzoyl)-α-D-galactopyranosidurononitrile (7b)

IR ($CHCl_3$): 3020, 1740 (C=O), 1680, 1510, 1370, 1340, 1240, 1210, 1170, 1130, 1070, 1040, 935, 700 cm^{-1}.-^1H NMR (400 MHz, pyridine-d_5, T = 308 K): *unit E*, δ = 5.84 (d, 1-H, $J_{1,2}$ = 8.4 Hz), 3.92 (ddd, 2-H, $J_{2,3}$ = 10.4 Hz), 6.17 (dd, 3-H, $J_{3,4}$ = 9.2 Hz), 5.34 (dd, 4-H, $J_{4,5}$ = 10.0 Hz), 3.87 (ddd, 5-H, $J_{5,6}$ = 2.8 Hz), 4.32 (dd, 6-H), 4.44 (dd, 6-H', $J_{5,6'}$ = 5.2 Hz, $^2J_{6,6'}$ = 12.0 Hz), 1.97, 2.00, 2.06, 2.07 (4*s, 4*$COCH_3$), 9.16 (d, N<u>H</u>$COCH_3$, $J_{NH,2}$ = 7.6 Hz); *unit F*, δ = 5.78 (d, 1-H, $J_{1,2}$ = 3.2 Hz), about 4.8 (2-H, covered by the water signal), 6.10 (dd, 3-H, $J_{2,3}$ = 10.4 Hz), 6.60 (dd, 4-H, $J_{3,4}$ = 3.6 Hz), 5.76 (d, 5-H, $J_{4,5}$ = 1.6 Hz); *3-Trifluoromethylbenzoyl group*, δ = 8.44 (s, 2-H), 8.34 (d, J = 8.0 Hz) and 7.78 (d, J = 7.6 Hz, 4-H and 6-H), 7.38 (dd, 5-H).- ^{13}C NMR (75.4 MHz, pyridine-d_5, C,H COSY; APT; T = 308 K): *unit E*, δ = 101.80 (C-1), 56.43 (C-2), 72.22 (C-3), 69.72 (C-4), 71.93 (C-5), 62.37 (C-6), 20.29, 20.35, 20.44 (3*CO<u>C</u>H_3), 23.05 (NHCO<u>C</u>H_3), 169.66, 170.17, 170.25, 170.80 (4*<u>C</u>OCH_3); *unit F*, δ = 99.53 (C-1), 75.77 (C-2), 67.75 (C-3), 71.14 (C-4), 60.91 (C-5), 117.67 and 116.11 (C-3^{all} and CN), 156.63 ($OCONH_2$); *3-trifluoromethylbenzoyl group*, δ = 130.40 (C-1), 126.66 (C-2, $^3J_{C,F}$ = 3.5 Hz), 130.72 (C-3, $^2J_{C,F}$ = 32.0 Hz), 133.93, 133.39 and 130.07 (C-2^{all}, C-4 and C-6), 129.86 (C-5), 123.91 CF_3 ($^1J_{C,F}$ = 276.8 Hz), 164.20 ($CO^{benzoyl}$).- ^{19}F NMR (282.3 MHz, pyridine-d_5, T = 308 K): δ = 15.34, 15.57 CF_3 signals.- $C_{32}H_{36}N_3O_{15}F_3$ (759.64, 759.21), FAB-MS (3-nitrobenzyl alcohol): m/z = 782.4 ([M+Na]$^+$), 760.4 ([M+H]$^+$), 702.3 ([M+H-AllOH]$^+$), 330.1 ([e]$^+$).

Conversion of 3 to 4a by Saito reaction

3 (0.098 g, 0.126 mmol), MCZ (0.066 g, 0.367 mmol) and $Mg(ClO_4)_2$ (0.226 g, 1.012 mmol) were dissolved in 10:1 2-propanol–water (25 ml, sonication). The solution was flushed with argon and then irradiated for 2d at 257 nm (quartz reaction vessels, Rayonet reactor). Progress of the reaction was monitored by TLC ($CHCl_3$–MeOH 3:1). After solvent evaporation the residue was partitioned between water and CH_2Cl_2 and water. **4a** was in the aqueous and educt **3** in the organic phase. The aqueous phase was concentrated and then freed from magnesium perchlorate by gel filtration (Sephadex G 10®, MeOH–H_2O 1:1, flash pump) to give pure **4a** (71 mg, 95 %). The spectral data were identical with those of the sample described above.

Wacker oxidation of 4a

a) Oxygen was bubbled into a mixture containing **4a** (10.0 mg, 17 μmol), 1: 1 DMF-H_2O (330 μl), palladium(II) chloride (0.8 mg, 4 μmol), and copper(I) chloride (5.0 mg, 51 μmol) for 6 h at 45°C. Then a second portion of palladium(II) chloride (0.25 eq) was added and the reaction was continued for 2 h. Filtration through silica gel (1 g, elution with $CHCl_3$-MeOH 6:1), followed by solvent evaporation and LC (silica gel (1 g), covered with Florisil (0.2 g), $CHCl_3$-MeOH 6: 1) yield a mixture (8.6 mg) of a 2.5:1:1 mixture (determined by NMR) of **4b**, aldehyde **4c** and **4d** (formed by degradation of the labile aldehyde).

b) A mixture of **4a** (64.5 mg, 109 μmol), 1:1 DMF- H_2O (3.1 ml), and palladium(II) chloride (24.8 mg, 139 μmol) was stirred at 45°C for 4 h. Excess of oxidant was destroyed with allyl alcohol (20 μl, stirring at 45°C h for 3 h). After water addition and lyophilization the residue was taken up in acetonitrile and un-

soluble components were removed by filtration. MPLC ($CHCl_3$-MeOH 10:1 → 8:1) provided **4b** (10.9 mg, 17%), **4d** (4.7 mg, 8%), and a fraction containing both compounds (2.7 mg).

2-Oxopropyl 2-*O*-(2-acetamido -3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-3-*O*-carbamoyl-4-deoxy-α-D-*xylo*-hexopyranosiduronamide (4b)

IR (KBr): 3463, 3369, 2932, 2361, 1746 (C=O), 1682 ($CONH_2$), 1605, 1551, 1376, 1331, 1233, 1076, 1043, 930 cm^{-1}.-^{1}H NMR (400 MHz, pyridine-d_5): *unit E*, δ = 5.64 (d,1-H, $J_{1,2}$ = 8.4 Hz), 3.95-4.00 (m, 2-H), 6.16 (dd, 3-H, $J_{2,3} = J_{3,4}$ = 10.0 Hz), 5.40 (dd, 4-H, $J_{3,4} = J_{4,5}$ = 10.0 Hz), 3.95-4.00 (m, 5-H), 4.43 (m, 6-H, 6-H'), 1.99, 2.02, 2.03, 2.15, 2.17 (5s, $COCH_3$ and OCH_2COCH_3), 9.22 (d, $NHCOCH_3$, $J_{NH,2}$ = 7.7 Hz); *unit F*, δ = 5.46 (d, 1-H, $J_{1,2}$ = 3.3 Hz), 4.02 (dd, 2-H, $J_{2,3}$ = 10.0 Hz), 5.80 (ddd, 3-H, $J_{2,3} = J_{3,4ax}$ = 10.0 Hz, $J_{3,4eq}$ = 5.1 Hz), about 1.94 (m, 4-H_{ax}, hidden by $COCH_3$ signals), 3.16 (ddd, 4-H_{eq}, $J_{4ax,4eq}$ = 13.0 Hz), 4.78 (dd, 5-H, $J_{4ax,5}$ = 12.5 Hz), 7.89 (s, b, $CONH_2$), 8.43 (s, b, $CONH_2$); *2-oxopropyl group*, δ = 4.20, 4.28 (AB, OCH_2COCH_3, $J_{A,B}$ = 17.0 Hz).- ^{13}C NMR (100.6 MHz, pyridine-d_5): *unit E*, δ = 101.74 (C-1), 56.02 (C-2), 72.34 (C-3), 69.39 (C-4), 71.71 (C-5), 61.89 (C-6), 20.23, 20.32, 20.36, 23.03 ($COCH_3$), 168.94, 169.58, 170.17, 170.33, 170.83, 172.51 (CO); *unit F*, δ = 100.29 (C-1), 79.65 (C-2), 68.85 (C-3), 34.97 (C-4), 68.42 (C-5), *see under unit E*, $CONH_2$, 157.13 ($OCONH_2$), *2-oxopropyl group*, δ = 26.52 (OCH_2COCH_3), 73.91 (OCH_2COCH_3), 206.68 (OCH_2COCH_3). In the CO region there is one (unexplained) extra signal.- $C_{24}H_{35}N_3O_{15}$ (605.55, 605.21), FAB-MS (lactic acid): m/z = 606.1 ($[M+H]^+$), 330.1 ($[e]^+$).

3-Oxopropyl 2-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-3-*O*-carbamoyl-4-deoxy-α-D-*xylo*-hexopyranosiduronamide (4c)

^{1}H NMR (400 MHz, pyridine-d_5): The following signals of **4c** could be identified in the spectrum of the mixture of **4b**, **4c** and the free sugar **4d** (ratio 2.5:1:1): δ = 4.72 (dd, 5-H^F), 5.43 (d, 1-H^F $J_{1,2}$ = 3.0 Hz), 9.21 (d, $NHCOCH_3$, $J_{NH,2}$ = 8.0 Hz), 9.73 (t, OCH_2CH_2CHO, J = 1.5 Hz).

2-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-3-*O*-carbamoyl-4-deoxy-α-D-xylo-hexopyranuronamide (4d)

^{1}H NMR (400 MHz, pyridine-d_5): *unit E*, δ = 5.67 (d, 1-H, $J_{1,2}$ = 8.5 Hz), 3.93-4.01 (m, 2-H), 6.14 (dd, 3-H, $J_{2,3} = J_{3,4}$ = 10.0 Hz), 5.35 (dd, 4-H, $J_{3,4} = J_{4,5}$ = 10.0 Hz), 3.93-4.01 (m, 5-H), 4.32 (dd, 6-H, $J_{5,6}$ = 2.5 Hz), 4.47 (dd, 6-H', $^2J_{6,6'}$ = 12.3 Hz, $J_{5,6'}$ = 5.0 Hz), 1.92, 1.98, 1.99, 2.15 (4s, $COCH_3$), 9.05 (d, $NHCOCH_3$, $J_{NH,2}$ = 8.0 Hz); *unit F*, δ = 6.02 (d, 1-H, $J_{1,2}$ = 3.0 Hz), 4.12 (dd, 2-H, $J_{2,3}$ = 10.0 Hz), 5.99 (ddd, 3-H, $J_{2,3} = J_{3,4ax}$ = 10.0 Hz, $J_{3,4eq}$ = 5.0 Hz), 1.94-2.04 (m, 4-H_{ax}, hidden by $COCH_3$ signals), 3.28 (ddd, 4-H_{eq}, $J_{4ax,4eq}$ = 13.0 Hz), 5.16 (dd, 5-H, $J_{4ax,5}$ = 12.5 Hz, $J_{4eq,5}$ = 2.5 Hz), 7.86 (d, $CONH_2$), 8.33 (d, $CONH_2$), 7.39 ($OCONH_2$, ?).

Reaction of 4a with palladium(II) chloride and subsequent photolysis

A mixture of **4a** (14.9 mg, 25 μmol), 1:1 DMF- H_2O (500 μl), and palladium(II) chloride (6.2 mg, 35 μmol) was stirred at 50°C for 2 h. Excess of oxidant was destroyed with allyl alcohol (6 μl, stirring at 40°C h for 2 h). After water addition and lyophilization the residue was taken up in acetonitrile and unsoluble components were removed by filtration. Solvent evaporation and LC ($CHCl_3$-MeOH 9:1) gave a mixture of **4b** and **4c**, and the deallylated sugar **4d** (7.7 mg, ≈ 51%). This mixture was dissolved in acetonitrile (15 ml) and the solution was flushed with argon (40 min). Then triethylamine was added and the solution was irradiated (Hg high pressure lamp, quartz reaction vessel) for 1 h. Solvent evaporation followed by LC (1 g of silica gel,

$CHCl_3$-MeOH 10:1) provided slightly impure deallylated sugar **4d** (6.2 mg, 44%, based on allyl protected sugar **4a**).

Deallylation with freshely prepared tetrakis(triphenylphosphine)palladium-(0)

To a solution of **4a** (36 mg, 0.061 mmol) in 99 per cent acetic acid (1 ml, carefully degassed by sonication) a suspension of freshly prepared tetrakis(triphenylphosphine)palladium-(0) (0.057 g, 0.049 mmol) in 99 per cent acetic acid (3 ml, degassed) was added and the mixture was stirred at 20°C for 3 h. Then TLC ($CHCl_3$–MeOH 3:1, visualization by UV light and anisaldehyde reagent) indicated complete conversion. Acetic acid was removed by codistillation with toluene. The residue was partioned between $CHCl_3$ and water. The aqueous phase was washed with water and then freeze-dried to give a light-yellow residue. The raw products of two experiments (56 mg and 5 mg, respectively) could partly be purified by LC ($CHCl_3$–MeOH 5:1) to give **4d** (9 mg, about 27%, slightly contaminated). **4d** was unsoluble in $CHCl_3$, CH_2Cl_2, MeOH, H_2O, pyridine and could be dissolved in 1:1 MeOH–H_2O (8 mg in 50 ml).- ^{13}C NMR of an impure sample (100 MHz, pyridine-d_5): δ = 14.10 (?), 19.04, 36.35, 36.44, 36.64, 57.33 (C-2^E), 62.62 (C-6^E), 69.60, 70.85, 72.40, 73.23, 74.73, 76.54, 79.85, 81.24, 82.77, 94.41 (C-1^F, **4d**), 100.95, 101.65, 122.10, 126.81, 128.31,128.52, 128.68, 129.14, 129.29, 130.21, 138.79, 139.12, 152.19, 152.21, 154.15, 154.16, 163.69, 163.71, 164.97, 165.03, 165.07, 172.66, 172.67, 172.74, 172.80, 173.52, 173.54, 173.57, 173.58 ppm.- ^{31}P NMR (81.0 MHz, pyridine-d_5): δ = 1.47 ppm (impurity).- $C_{21}H_{31}N_3O_{14}$ (549.48, 549.18), FAB-MS: m/z = 572.1 $[M+Na]^+$, 550.1 $[M+H]^+$, 330.1 $[e]^+$

2-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-3-*O*-carbamoyl-4-*O*-(3-(trifluoromethyl)-benzoyl)-α-D-galactopyranuronamide (5)

In an atmosphere of argon to a solution of **3** (0.335 g, 0.431 mmol) and $Pd(PPh_3)_4$ (0.399 g, 0.345 mmol) in 4:3 acetic acid-toluene (35 ml, degassed by sonication) was stirred at 20°C for 30 min. Progress of the reaction was followed by TLC ($CHCl_3$–MeOH 3:1). Acetic acid was removed by codistillation with toluene. The residue was redissolved in water and freeze-dried. Repeated FC (acetone–$CHCl_3$ 7:3) provided **5** (267 mg, 83 %) as a anomeric mixture containing only traces of the ß-isomer.- IR (KBr): 3614–3393 (OH), 1739, 1684, 1546, 1248 cm^{-1}.- ^1H NMR (400 MHz, acetone-d_6, H,H COSY): δ = 1.76, 1.86, 1.91, ca.1.99, (CH_3 signals), 3.68–3.78 (m, 2H, 2-H^E, 5-H^E), 4.01 (dd, 1H, 2-H^F, $J_{1F,2F}$ = 3.2 Hz, $J_{2F,3F}$ = 10.8 Hz), 4.09 (d, 2H, 6-H^E, $J_{5E,6E}$ = 2.7 Hz, $J_{6E,6'E}$ = 12.2 Hz), 4.19 (d, 1H, 6-H'^E, $J_{5E,6'E}$ = 5.0 Hz, $J_{6E,6'E}$ = 12.2 Hz), 4.71 (d, 1H, 5-H^F, (α oder β), $J_{4F,5F}$ = 1.4 Hz), 4.88 (d, 1H, 1-H^E, $J_{1E,2E}$ = 8.1 Hz, hidden by the 4-H^E signal), 4.89 (t, 1H, 4-H^E, $J_{3E,4E}$ = $J_{4E,5E}$ = 10.2 Hz, hidden by the 1-H^E signal), 5.19 (dd, 1H, 3-H^E, $J_{2E,3E}$ = 10.2 Hz, $J_{3E,4E}$ = 9.6 Hz), 5.26 (dd, 1H, 3-H^F, $J_{2F,3F}$ = 10.6 Hz, , $J_{3F,4F}$ = 3.6 Hz), 5.53 (dd, 1H, 1-H^F, $J_{1OH,1F}$ = $J_{1F,2F}$ ca. 4 Hz), 6.02 (dd, 1H, 4-H^F, $J_{3F,4F}$ = 3.5 Hz, $J_{4F,5F}$ = 1.4 Hz), 6.15 (d, 1H, 1α-OH^F, $J_{1OH,1F}$ ca. 4 Hz), 6.60 (s, b, 1H, $CONH_2$), 6.79 (d, 1H, N<u>H</u>$COCH_3$, $J_{NH,2E}$ = 8.8 Hz), 6.96 (s, b, 1H, $CONH_2$), 7.76 (t, 1H, 5-$H^{trifluoromethylbenzoyl\ (Tfmb)}$, $^3J_{4Tfmb,\ 5Tfmb}$ = $J_{5Tfmb,\ 6Tfmb}$ = 7.8 Hz), 7.90 - 8.01 (m, 1H, 4-H^{Tfmb}), 8.14–8.29 (m, 2H, 2-H^{Tfmb}, 6-H^{Tfmb}).-^{13}C NMR (50.3 MHz, acetone-d_6, DEPT, APT): δ = 20.11, 20.14, 20.35, 22.56 (3 CO<u>C</u>H_3, NHCO<u>C</u>H_3), 54.73 (CH, C-2^E), 62.34 (CH_2, C-6^E), 69.45 (CH), 69.63 (CH), 69.63 (CH), 71.90 (CH), 71.90 (CH), 72.88 (CH), 76.10 (CH), 93.33 (CH, C-1^F), 102.56 (CH, C-1^E), 124.44 (CH, $CF_3{}^{Tfmb}$, $^1J_{C,F}$ = 272.0 Hz), 126.43 (d, CH, C-2^{Tfmb}), 130.19 (CH, C-4^{Tfmb}), 130.48 (CH, C-5^{Tfmb}), 130.97 (d, <u>C</u>-CF_3, $^2J_{C,F}$ = 32.7 Hz), 131.87 (C-1^{Tfmb}), 133,80 (CH, C-6^{Tfmb}), 156.36 ($OCONH_2$), 164.10 (OCO^{Tfmb}), 169.74 ($CONH_2$), 169.88, 170.30, 170.34, 170.55 (4 <u>C</u>OCH_3).-^{19}F NMR (188.2 MHz, acetone-d_6): δ = -0.515.- $C_{29}H_{34}F_3N_3O_{16}$

(737.59, 737.19), MALDI: m/z = 776.2 $[M+K]^+$, 760.2 $[M+Na]^+$, FAB-HR-MS: $[M+H]^+$ calc: 738.1969, found: 738.1977.

2-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-3-*O*-carbamoyl-1-*O*-{[(R)-2-methoxycarbonyl-2-(3,8,8,11,14,18-hexa-methylnonadecyloxy)-ethoxy]-(2,2,2-trichloro-1,1-dimethylethoxy)-phosphoryl}-4-*O*-(3-(trifluoromethyl)-benzoyl)-α-D-galactopyranuronamide (10)

To a solution of dried 1H-1,2,4-triazole (0.095 g, 1.372 mmol) in 4:1 CH_2Cl_2-pyridine (4.4 ml) at 0°C 2,2,2-trichloro-1,1-dimethylethyldichloro phosphite (68 µl, 0.095 g 0.342 mmol) was added and the mixture was stirred at 0°C for 40 min. Then a solution of **5** (0.230 g, 0.312 mmol) in 4:1 CH_2Cl_2 - pyridine (3.4 ml) was added and the reaction mixture was stirred at 0°C for 3 h. Within 1.5 h a solution of **6** (0.440 g, 0.934 mmol) in 4:1 CH_2Cl_2 - pyridine (3.7 ml) was added in three portions. After another 1.5 h bis-(trimethylsilyl)-peroxide (96 µl (0.452 mmol) was added, the mixture allowed to warm to ambient temperature and stirred at this temperature overnight. Progress of all steps was monitored by TLC ($CHCl_3$–MeOH 10:1). Toluene was added and solvents were distilled off. Repeated FC ($CHCl_3$-methanol 10:1) yielded **10** (0.261 g, 58 %).- IR (KBr): 3440–3429, 1743, 1683, 1247 cm^{-1}.- ^1H NMR (400 MHz, pyridine-d_5, H,H COSY): δ = 0.80–1.90 (signals from unit I), 1.99, 2.06, 2.13, 2.15, 2.19, 2.19 ($COCH_3$- and $C(CH_3)_2CCl_3$ signals), 3.61–3.71 (m, 1H, 1-H^{I}), 3.76 (s, 3H, $COOCH_3$), 3.82 –3.89 (m, 2H, 1-$H^{'I}$, 5-H^E), 3.91–4.06 (m, 1H, 2-H^E), 4.28–4.36 (dd, 1H, 6-H^E, $^2J_{6E,6'E}$ = 12.4 Hz), 4.45–4.51 (m, 2H, 2-H^H, 6-$H^{'E}$), 4.67–4.76 (m, 1H, 1-H^H), 4.78–4.86 (m, 1H, 1-$H^{'H}$), 5.05 (hidden by the H_2O, 2-H^F), 5.43–5.53 (m, 2H, 4-H^E, 5-H^F), 5.91 (d, 1H, 1-H^E, $^3J_{1E,2E}$ = 8.1 Hz), 6.17–6.27 (m, 2H, 3-H^E, 3-H^F), 6.86 (s, 1H, 1-H^F), 6.98–7.02 (m, 1H, 4-H^F), 7.23–7.29 (m, 1H, 5-H^{Tfmb}), 7.69 (d, 1H, 4-H^{Tfmb}, $^3J_{4Tfmb,\ 5Tfmb}$ = 4.4 Hz), 7.70–7.96 (s, b, 2H, $OCONH_2$), 8.21 (d, 1H, 6-H^{Tfmb}, $J_{5Tfmb,\ 6Tfmb}$ = 7.8 Hz), 8.32–8.42 (m, 2H, 2-H^{Tfmb}, $CONH_2$), 8.82 (s, b, 1H, $CONH_2$), 9.37 (d, 1H, N<u>H</u>$COCH_3$, $J_{NH,2E}$ = 7.8 Hz).- ^{13}C NMR (50.3 MHz, pyridine-d_5, DEPT, C,H COSY): δ = 19.88 (CH_3), 20.07 (CH_3), 20.23 (CH_3), 20.37 (d, CH_3, $J_{C,P}$ = 1.8 Hz), 20.50 (CH_3), 20.79 (CH_3), 20.88 (CH_3), 21.10 (CH_3), 23.05 (CH_3), 23,14 (CH_3) , 23.56, 24.05 (CH_3), 25.07 (CH_2), 25.38 (CH_2), 25.42 (CH_2), 27.76 (CH_3), 28.49 (CH), 28.64 (CH_2), 30.44 (CH), 30.49 (CH), 31.52 (CH_2), 31.80 (CH_2), 32.99 (C-8^I), 33.68 (CH), 34.46 (CH), 34.90 (CH_2), 34.97 (CH_2), 37.72 (CH_2), 37.39 (CH_2), 39.72 (CH_2), 39.76 (CH_2), 39.87 (CH_2), 37.97 (CH_2), 42.58 (CH_2), 52.50 ($COO\underline{C}H_3$), 56.70 (CH, C-2^E), 62.70 (CH_2, C-6^E), 68.68 (d, CH_2), 69.06 (CH), 70.00 (CH, C-4^E), 70.18 (CH_2), 72.10 (CH, C-4^F), 72.20 (CH, C-5^E), 72.57 (CH, C-5^F), 72.73 (CH), 76.35 (d, CH, C-2^F, $^3J_{C,P}$ = 11.0 Hz), 78.63 (d, CH, C-2^H, $^3J_{C,P}$ = 8.2 Hz), 91.03 (d, <u>C</u>$(CH_3)_2$ CCl_3), 91.08, 98.51 (splitting pattern, CH, C-1^F), 102.65 (CH, C-1^E (β)), 106.70 (CCl_3), 124.38 (CF_3^{Tfmb}, $^1J_{C,F}$ = 272.7 Hz), 127.09 (CH, C-2^{Tfmb}), 129.96 (CH, C-5^{Tfmb}), 130.00 (CH) and 133.77 (CH, C-4^{Tfmb} and C-6^{Tfmb}), 130.86 (CCF_3, $^2J_{C,F}$ = 32.5 Hz), 131.66 (C-1^{Tfmb}157.24 ($OCONH_2$), 164.56 (OCO^{Tfmb}), 169.51 ($CONH_2$), 170.18, 170.69, 170.98, 171.31 ($COCH_3$).- ^{31}P NMR (81.0 MHz, pyridine-d_5): δ = -4.64.- ^{19}F NMR (188.2 MHz, pyridine-d_5): δ = 15.36.- $C_{62}H_{96}Cl_3F_3N_3O_{22}P$ (1429.77, 1427.52), FAB-MS: m/z = 1450 $[M+Na]^+$, 742.2 $[f-H+Na]^+$, 330.0 $[e]^+$.- HR-MS: $[M+Na]^+$ calc: 1450.5139, found: 1450.5163.

2-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-3-*O*-carbamoyl-4-deoxy -1-*O*-{[(R)-2-methoxycarbonyl-2-(3,8,8,11,14,18-hexamethylnonadecyloxy)-ethoxy]-(2,2-dichloro-1,1-dimethylethoxy)-phosphoryl}-α-D-xylohexopyranuronamide (12)

10 (10 mg, 6.998 µmol), MCZ (7 mg, 0.020 mmol), and $Mg(ClO_4)_2$ (12 mg, 0.056 mmol) were dissolved in in 10:1:1 isopropanol–water–hexanes (15 ml, degassed by sonication) and the mixture was flushed with argon for 15 min. The solution was irradiated at 257.3 nm (Rayonet reactor, quartz vessel) for 3 h. Progress

of the reaction was monitored by TLC ($CHCl_3$–MeOH 5:1). After solvent evaporation the residue was partioned between water and $CHCl_3$. The aqueous phase was carefully extracted with $CHCl_3$. Usual workup of the combined organic phases and FC ($CHCl_3$-methanol 10:1) provided **12** (4 mg, 47 %).- ^{1}H NMR (400 MHz, pyridine-d_5, ^{1}H,^{1} H COSY): δ = 0.82–1.72 (unit I signals with 1.45–1.57 (m, 1H, 2^I-H)), 1.72 - 1.82 (m, 1H, 2$^{'I}$-H), 1.85, 1.92, 2.01, 2.06, 2.15, 2.18 ($COCH_3$- and $C(CH_3)_2$ $CHCl_2$ signals and 4-H^{F,ax}), 3.12–3.20 (m, 1H, 4-H^{F,eq}), 3.61–3.70 (m, 1H, 1-H^I), 3.78 (s, 3H, $COOCH_3$), 3.79–3.82 (m, 1H, 1-H$^{'I}$, hidden by the $COOCH_3$ signal), 3.83–3.92 (m, 1H, 5-H^E), 3.97–4.04 (m, 1H, 2-H^E), 4.04–4.15 (m, 1H, 2-H^F), 4.42 (dd, 1H, 6-H^E, $J_{5E,6E}$ = 1.8 Hz, $^3J_{6E,6'E}$ = 12.5 Hz), 4.48 (t, 1H, 2-H^H, $^3J_{1H,2H}$ = 4.6 Hz), 4.57 (dd, 1H, 6 –H$^{'E}$ $^3J_{5E,6'E}$ = 4.2 Hz, $^3J_{6E,6'E}$ = 12.2 Hz), 4.61–4.70 (m, 1H, 1-H^H), 4.71–4.80 (m, 1H, 1-H$^{'H}$), 5.46 (t, 1H, 4-H^E, $J_{3E,4E}$ = $J_{4E,5E}$ = 9.9 Hz), 5.65 (d, 1H, 1-H^E, $J_{1E,2E}$ = 8.1 Hz), 5.75 (dt, 1H, 3-H^F, $J_{2F,3F}$ = $J_{3F,4Fax}$ = 10.9 Hz, $J_{3F,4Feq}$ = 5.3 Hz), 6.17 (dd, 1H, 3-H^E, $J_{2E,3E}$ and $J_{3E,4E}$ = 9.2 Hz and 10.6 Hz, respectively), 6.46–6.52 (m, 1H, 1-H^F), 6.56 (s, 1H, $CHCl_2$), 7.90 (s, b, $CONH_2$), 8.54 (s, b, $CONH_2$), 9.16 (d, 1H, N<u>H</u>$COCH_3$, $J_{NH,2E}$ = 8.1 Hz).- ^{13}C NMR (50.3 MHz, pyridine-d_5, DEPT,): δ = 19.26 (CH_3), 19.42 (CH_3), 19.61 (CH_3), 19.73 (d, CH_3, $J_{C,P}$ = 1.8 Hz), 19.86 (CH_3), 20.19 (CH_3), 20.26 (CH_3), 20.43 (CH_3), 22.41 (CH_3), 22.52 (CH_3), 22.97 (CH_3), 23.26 (CH_3), 23.32 (CH_2), 24.42 (CH_2), 24.76 (CH_2), 27.12 (CH_3), 27.87 (CH), 28.01 (CH_2), 29.82 (CH), 29.87 (CH), 30.87 (CH_2), 31.16 (CH_2), 32.36 (C-8^I), 33.02 (CH), 33.84 (CH), 34.27 (CH_2), 34.33 (CH_2), 36.77 (CH_2), 37.10 (CH_2), 37.13 (CH_2), 37.35 (CH), 39.11 (CH_2), 39.22 (CH_2), 41.95 (CH_2), 51.87 ($COOCH_3$), 55.78 (CH, C-2^E), 62.14 (CH_2, C-6^E), 67.82 (d, CH_2, $J_{C,P}$ = 7.3 Hz), 68.27, 69.40, 69.53 (d, CH_2), 69.71, 71.67 (CH), 72.31 (CH), 78.00 (d, CH_2, $J_{C,P}$ = 8.2 Hz), 78.44 (d, CH_2, $J_{C,P}$ = 7.3 Hz), 78.89 (d, CH_2, $J_{C,P}$ = 10.0 Hz), 85.78 (d, <u>C</u>$(CH_3)_2CHCl_2$, $J_{C,P}$ = 6.3 Hz), 98.03 (CH, C-1^F (α), $^2J_{C,P}$ = 6.4 Hz), 101.97 (CH, C-1^E (β)), 105.05 ($CHCl_2$), 156.77 ($OCONH_2$), 169.50, 169.54, 170.12, 170.38, 170.69, 171.45 ($COCH_3$).- ^{31}P NMR (81.0 MHz, pyridine-d_5): δ = -4.61, 4.03.- $C_{54}H_{94}Cl_2N_3O_{20}P$ (1207.22, 1205.55), FAB-MS: m/z = 1228.6 $[M+Na]^+$, 1206.8 $[M+H]^+$, 554.1 $[f\text{-}H+Na]^+$, 471.1 $[f\text{-}H_2NCOOH]^+$, 411.1 $[f\text{-}H_2NCOOH\text{-}AcOH]^+$, 330.1 $[e]^+$.-HR-MS: $[M+Na]^+$ calc: 1228.5443, found: 1228.5254.

Treatment of 12 with Zn-Cu couple

A mixture of **12** (22 mg, 0.018 mmol), Zn-Cu couple (25 mg), 2,4-pentanedione (29 µl, 0.285 mmol), and pyridine (1.2 ml) was stirred at 20°C overnight. TLC ($CHCl_3$–MeOH 5:1) indicated that practically no reaction had occurred.

2-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy -β-D-glucopyranosyl)-3-*O*-carbamoyl-1-*O*-{[(R)-2-methoxycarbonyl-2-(3,8,8,11,14,18-hexamethylnonadecyloxy)-ethoxy]-hydroxyphosphoryl}-4-*O*-(3-(trifluoromethyl)-benzoyl)-α-D-galactopyranuronamide (11)

10 (63 mg, 0.044 mmol), Zn-Cu couple (62 mg), and 2,4-pentanedione (74 µl, 0.251 mmol) in dry pyridine (3.4 ml) were stirred at 20°C for 1 h. TLC ($CHCl_3$–MeOH 5:1) showed completion of the reaction. Solids were removed by filtration and were carefully washed with methanol. After solvent evaporation (codistillation with toluene) the residue was dissolved in methanol-water 3:1 (20 ml). Dowex 50 WX 2 (H^+) (0.600 g) was added and the mixture was stirred at 20°C for 1 h. Filtration, washing the resin several times with methanol, solvent evaporation and FC (toluene-$CHCl_3$-methanol 4:4:3) provided **11** (56 mg, 100 %).- IR (KBr): 3615–3429, 1743, 1683, 1249 cm^{-1}.- ^{1}H NMR (200 MHz, pyridine-d_5,): Only broad signals which could not be assigned.-^{13}C NMR (100 MHz, pyridine-d_5,): δ = 19.00–44.00 (CH_3-, CH_2- and CH signals), 52.04 ($COO\underline{C}H_3$), 55.36 (C-2^E), 62.46 (C-6^E), 66.31, 69.83, 71.05, 72.05, 72.76, 79.50, 95.81 (C-1^F (α)), 101.61 (C-1^E (β)), 124.20 (CF_3^{Tfmb}, $^1J_{C,F}$ = 270.8 Hz), 128.26 (CH, C-2^{Tfmb}), 129.80 (2 CH) and 133.53 (CH,

C-5^{Tfmb}, C-4^{Tfmb}, C-$6^{Tfmb)}$,), 130.59 (CCF_3, $^2J_{C,F}$ = 32.6 Hz), 131.60 (C-1^{Tfmb}), 157.15 ($OCONH_2$), 164.39 (OCO^{Tfmb}), 169.74, 170.31, 170.58, 170.83, 171.83 ($COCH_3$)- ^{31}P NMR (81.0 MHz, pyridine-d_5): δ = -1.05 ppm.- ^{19}F NMR (188.2 MHz, pyridine-d_5): δ = 15.38 ppm.- $C_{58}H_{91}F_3N_3O_{22}P$ (1270.33, 1269.58), FAB-MS: m/z = 1314.7 $[M+2Na-H]^+$, 1292.7 $[M+Na]^+$, 742.1 $[f-H+Na]^+$.- HR-MS: $[M+2Na-H]^+$ calc 1314.5501, found 1314.5472, $[M+Na]^+$ calc 1292.5682, found 1292.5658.

2-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-3-*O*-carbamoyl-4-deoxy -1-*O*-{[(R)-2-methoxycarbonyl-2-(3,8,8,11,14,18-hexamethylnonadecyloxy)-ethoxy]-hydroxyphosphoryl}-α-D-xylo-hexopyranuronamide (13a)

11 (29 mg, 0.022 μmol), MCZ (12 mg, 0.066 mmol) and $Mg(ClO_4)_2$ (41 mg, 0.183 mmol) in 2-propanol-water 10:1 (20 ml, degassed by sonication) were irradiated as described above. After 1 h (TLC control, $CHCl_3$–methanol–toluene 1:1:1) solvents were evaporated and the residue was separated by FC (toluene-$CHCl_3$-methanol 4:4:3) to yield **13a** (0.017 g, 68 %).- ^1H NMR (200 MHz, pyridine-d_5, in the region of the sugar proton signals only broad signals appeared which could not be assigned): δ = 0.70–1.90 (unit I signals), 1.98, 2.03, 2.12, 2.24 ($COCH_3$ signals), 3.00–3.20 (m, b, 4-$H^{F)}$, 3.50–3.90 (broad m with s at 3.76, $COOCH_3$).- ^{13}C NMR (50.3 MHz, pyridine-d_5,): δ = 19.50–43.00 (CH_3-, CH_2- and CH signals), 52.25 ($COO\underline{C}H_3$), 70.01, 70.15, 157.86 ($OCONH_2$), 170.05, 170.86, 171.21, 172.16 ($COCH_3$ signals).- ^{31}P NMR (81.0 MHz, pyridine-d_5): δ = 0.20.- $C_{50}H_{88}N_3O_{20}P$ (1082.23, 1081.57), FAB-MS: m/z = 1120.8 $[M+K]^+$, 1104.8 $[M+Na]^+$, 330.2 $[e]^+$.

Deacylation of 13a

A turbid mixture of **13a** (0.025 g, 0.026 mmol) and 2:1 MeOH–H_2O (8 ml) was cooled to 0°C. 1M LiOH (70 μl) was added and the reaction mixture was stirred at 20°C for 5 h (TLC control, $CHCl_3$–MeOH–H_2O 18:11:2.7). After addition of Dowex WX 2 (H^+ 0.5 g) the mixture was stirred at 20°C for 30 min. The resin was filterd off and carefully washed with 2:1 methanol-water and methanol. Solvent evaporation and FC ($CHCl_3$-methanol-water 18:11:1.5) gave **13b** (0.012 g, 55 %) and **13c** (0.008 g, 35 %).

2-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-3-*O*-carbamoyl-4-deoxy-1-*O*-{[(R)-2-carboxycarbonyl-2-(3,8,8,11,14,18-hexamethylnonadecyloxy)-ethoxy]-hydroxy-phosphoryl}-α-D-xylohexopyranuron-amide (13c)

13a (22 mg, 0.021 mmol) was dissolved in 2:1 MeOH-H_2O (8 ml, turbid solution). At 0°C 1M LiOH (40 μl) was added and the mixture was stirred at 20°C for 6 h. Then 1M LiOH (30 μl) and after 3 h another portion of 1M LiOH (20 μl) were added. After a total reaction time of 11 h TLC ($CHCl_3$–MeOH–H_2O 18:11:2.7) showed completion of the reaction. Dowex WX 2 (H^+, 0.8 g) was added and the mixture was stirred at 20°C for 30 min. Filtration, washing the resin several times with 2:1 methanol-water and methanol, solvent evaporation and FC ($CHCl_3$–MeOH–H_2O 18:11:1.5) provided **13c** (24 mg, 86 %).- ^{13}C NMR (100 MHz, CD_3OD–$CDCl_3$–D_2O 6:1:1): δ = 20.00–43.00 (CH_3-, CH_2- and CH signals), 62.33 (C-6^E), 64.23, 68.87, 9.90, 71.71, 73.68, 77.70, 80.78, 103.57 (C-1^E). Most of the sugar part signals could not be found (probably due to micelle formation). By Gauss multiplication signals at δ = 96.75 (C-1^F) and at 57.66, 66.75, 71.30 and 75.10 became discernible.- ^{31}P NMR (81 MHz, CD_3OD-d_1–$CDCl_3$–D_2O 6:1:1): δ = -0.47.- $C_{43}H_{80}N_3O_{17}P$ (942.09, 941.52), FAB-MS: m/z = 986.4 $[M+2Na-H]^+$, 964.4 $[M+Na]^+$, HR-MS: $[M+Na]^+$ calc: 964.5123, found: 964.5136.

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